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(21) International Application Number: PCT/US96/15686 (22) International Filing Date: 30 September 1996 (30.09.96) (30) Priority Data: 08/539,865 6 October 1995 (06.10.95) US (71) Applicants: THE REGENTS OF THE UNIVERSITY OF MICHIGAN [US/US]; 300 S. State Street, Ann Arbor, MI 48109 (US). MICRO-PAK, INC. [US/US]; 103 Springer Building, 3411 Silverside Road, Wilmington, DE 19810 (US). (72) Inventors: WEINER, Norman; 406 Linda Vista, Ann Arbor, MI 48103 (US). WALLACH, Donald, F., H.; 94 Dow Road, Hollis, NH 03049 (US).-EGBARIA, Kamel; 6414 Plainview Road, Gurnee, IL 60031 (US). CHANDRASEKHARAN, Ramachandran; 4448 Swiss Stone Lane East #2B, Ypsilanti, MI 48197 (US). (74) Agents: LOREN, Ralph, A. et al.; Lahive & Cockfield, 60 State Street, Boston, MA 02109 (US).		(81) Designated States: AU, CA, HU, JP, KR, MX, PL, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: STIMULATION OF HAIR FOLLICLES (57) Abstract A novel method and delivery system for therapeutic weak acid or base materials has been developed. The method and delivery system utilize a therapeutic material which is modified to make it more hydrophilic and encapsulated in a lipid vesicle, preferably a non-phospholipid lipid vesicle. The method and delivery system is particularly well suited to topical delivery of minoxidil.		

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STIMULATION OF HAIR FOLLICLES

Background of the Invention

5 The present invention concerns a preparation and method for topical administration of a drug into and/or through hair follicles. Using the preparation and method of the invention, significant amounts of weak acid or weak based drugs, e.g., minoxidil, may be delivered topically through the external skin surface.

10 The skin, particularly the horny layer, provides several functions including mechanical protection and a barrier against the transmittal of external substances into the internal tissues. However, this barrier effect causes difficulty in the topical administration of therapeutic drugs as well as unwanted substances. It has been generally accepted that the optimal means of transmitting drugs upon topical administration is through the lipid
15 compartment of the stratum corneum. Accordingly, two general approaches to improve penetration through the lipid component have been devised; first, reducing the molecular weight of the drug provides easier access to the internal tissues; and second, partitioning the drug into a lipid phase as compared with an aqueous phase should allow easier penetration through the lipid component of the stratum corneum. While the first approach, reducing the
20 molecular weight of the drug, has obvious advantages, it is often difficult to reduce the molecular weight without losing the activity of the drug. Therefore, much of the research on topical delivery of drugs has followed the second strategy, partitioning the drug into a lipid rather than an aqueous phase.

25 A number of different approaches have been attempted to achieve a favorable partition into the lipid rather than the aqueous phase. Since many of the drugs are either weak acids or bases, making the formulation at a pH such that the drug is in an unionized state where the solubility in the aqueous phase is normally decreased has been considered a preferable mode. Similarly, encapsulating a drug in a lipophilic rather than hydrophilic
30 phase has potential advantageous properties. This lipophilic phase can include lipid vesicles such as liposomes and lipid structures such as micelles.

 Accordingly, it has been theorized that the use of liposome should be a particularly advantageous in delivering drugs through the stratum corneum. Much of the earlier work
35 on liposomes, particularly those using phosphatidylcholine and phosphatidylserine as the wall materials, were attempts to simulate cellular membranes. The theory is that if one provides a drug to the skin in lipid systems similar to cellular membrane that is similar to the skin cells, the transition from the model system through the skin membranes, passage from this system through the skin should be facilitated. However, the use of liposomes as

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drug delivery vehicles have not normally improved drug permeation through the skin. Further, the amount of hydrophobic drug deposited into the dermis using liposomes has, in fact, been found to be lower than that obtained using simple solutions. Extensive in vivo and in vitro experiments on the penetration into the skin of various hydrophobic drugs such as progesterone, estradiol, hydrocortisone and cyclosporin-A after topical administration of drugs and liposomal formulas has shown that phospholipid liposomes do not improve penetration. Accordingly, conventional wisdom does not work in this type of system.

An example of a drug that has been problematic for topical delivery is minoxidil, 6-(1-Piperidinyl)-2,4-pyrimidinediamine 3-oxide. Minoxidil was originally used as a hypertensive agent so it was not generally used topically. However, it has recently been shown that topical solutions of minoxidil, sold under the trademark Rogaine[®], act as a hair growth stimulant. Rogaine is a 2% solution of minoxidil in an alcohol/propylene glycol/water mixture. Minoxidil is almost insoluble in acetone, chloroform, water or ethyl acetate. Although there is some penetration of the skin surface and hair follicles using this alcohol based solution of minoxidil, a way to improve its penetration should make a more effective hair growth preparation.

Accordingly, an object of the invention is to provide a method of providing better penetration into and across skin, and particularly into the hair follicles for topically administered drugs.

A further object of the invention is to provide a method and preparation which provides good penetration across skin through hair follicles in higher quantities than is presently known.

Another object of the invention is to provide a minoxidil preparation which has improved penetration into the hair follicles.

These and other objects and features of the invention will be apparent from the following description and the drawing.

Summary of the Invention

The present invention features a method of improving topical penetration of a therapeutic material such as a drug through the skin. The invention is based, in part, on the discovery that making a material hydrophilic, rather than hydrophobic, and encapsulating the

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drug in a lipid vesicle, can improve delivery. This is particularly pertinent to the delivery of minoxidil. Non-phospholipid lipid vesicles, particularly those having glycerol dilaurate as the primary lipid in the wall material, are preferred.

5 For a number of therapeutic materials, topical penetration of these materials into a skin portion having hair follicles can be improved by modifying the solubility of the therapeutic materials in aqueous solutions. The modified therapeutic material is encapsulated in a lipid vesicle and the lipid vesicle is delivered to the skin portion having hair follicles, whereby the hair follicles appear to act as a conduit for the therapeutic
10 material.

A number of different modifications can be made to the therapeutic material to provide the advantages of the invention. One such modification is ionizing the material by modifying the pH of a solution containing the material. Ionization improves aqueous
15 solubility. Similarly, the therapeutic material may be converted into a salt preferably by a reaction of the therapeutic material with an organic acid or base, most preferably an alpha-hydroxy acid such as lactic acid or a pharmaceutically acceptable derivative thereof. In other aspects, the salt could be made by reacting the therapeutic material with a dextrin such as a cyclodextrin.

20 As noted, preferred lipid vesicles are non-phospholipid lipid vesicles. These lipid vesicles are well known in the art and are described in patents such as United States Patent No. 4,911,928, United States Patent No. 5,032,457, and United States Patent No. 5,147,723, the disclosures of which are incorporated herein by reference. United States Patent
25 No. 5,260,065, the disclosure of which is also incorporated herein by reference, describes a preferred type of lipid vesicle. This patent describes lipid vesicles having blended lipid walls with a primary wall material selected from the group consisting of C₁₂-C₁₈ fatty alcohols, C₁₂-C₁₈ glycol monoesters, and C₁₂-C₁₈ glycerol mono and diesters. These materials appear to have particular potency in directing the modified therapy of materials
30 through the hair follicles. As noted previously, the preferred therapeutic material is minoxidil or a therapeutically effective derivative thereof. Using the minoxidil, the preferred wall material for vesicles has glycerol dilaurate as a primary lipid and polyoxyethylene 10 stearyl ether as a secondary wall material. The vesicles also may include cholesterol, phytosterol, or pharmaceutically acceptable derivatives thereof. The
35 preferred active is a reaction product of minoxidil and lactic acid (or lactate) which appears to have particular effectiveness. This minoxidil product acts as a pharmaceutical preparation for treatment of hair loss with advantageous effects.

The following description will more fully elucidate the invention.

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Detailed Description of the Invention

5 The present invention features the preparation and method for improved uptake of therapeutic materials by topical administration. The invention is particularly pertinent to delivery of minoxidil and other similar weak acids or weak bases. The invention is based, in part, on the discovery that by making these materials more hydrophilic, improved penetration through hair follicles could be achieved while minimizing the uptake by the lipid bilayer regions of the horny layer of the skin. This is contrary to standard topical
10 delivery concepts which say that the material should be made more hydrophobic so they are transmitted easier through the lipid compartment of the stratum corneum.

The method and preparation of the invention use lipid vesicles, primarily non-phospholipid lipid vesicles, to achieve this improved penetration. First, the materials
15 themselves are modified to make them more hydrophilic by reacting them with an acid or base, e.g., an organic acid or base such as lactic acid. In fact, the use of hydrophobic materials in lipid vesicles is contraindicated since they do not penetrate as well as the hydrophilic materials.

20 Another possible way of making the materials more hydrophilic is by placing them in a pH where they are ionized and therefore become more water soluble. That water-soluble material are transported to a greater extent by association with nonionic vesicles has been tested using carboxyfluorescein, TGF- α , interferon, and oligonucleotides. The present invention has particular usefulness in treating skin diseases of a follicular nature, such as
25 acne, alopecia areata and, using minoxidil, male pattern baldness. In addition, diseases without follicular involvement could be treated since the follicles could be used to transport the drugs to other regions of the dermis.

The mechanism for this delivery system appears to be the partitioning of the drugs
30 from the liposomal lipid bilayers into the skin after dehydration. This may account for the retardation of hydrophobic drug deposition into the skin, since the hydrophobic drugs stay in the lipid bilayer rather than penetrating the hair follicles.

The following examples more clearly illustrate the invention.

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Example 1

In this example, an oligonucleotide having a pK_a of about 9 is modified using a change in pH. The permeation of a charged drug across the stratum corneum is negligible

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if the skin lacks follicles, and there is only transport via the follicular route when the follicles were present. The material is encapsulated in a phospholipid lipid vesicle (or liposome) and the pH of the formulation was adjusted to 10-11. The liposomes were made with phosphatidylcholine, cholesterol and phosphatidylserine a molar ratio of 1:05:0.1 and total lipid concentration of 25 mg/ml. The results show that deposition of the oligonucleotide into the dermal layers is much higher at pH 10-11 than it is at either pH 7.4 or pH 3 in a buffered liposomal system. The amounts in the dermis of skin specimens with follicles were always much larger than those found in the dermis of skin without follicles. Accordingly, it clear that the follicular route is effective for transportation of hydrophilic materials in lipid vesicles across the stratum corium.

Example 2

In this example, phospholipid-based liposomes containing minoxidil were tested for stimulation of hair growth on balding stumptail Macaque monkeys. Minoxidil is very insoluble in water, organic solvents and oils. Conventional minoxidil preparations utilize a mixture of alcohol, propylene glycol, and water.

The minoxidil containing liposomes were prepared using the following procedure:

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Balding stumptail Macaque monkeys were treated for sixteen weeks with liposomes which contained minoxidil, a standard alcohol/propylene glycol/water preparation, or controls which included the liposomes or the preparation but did not contain minoxidil. Each monkey was treated once per day (5 days/week) on a one inch square of balding skin. The areas were shaved, the hair was collected, and weighed at four week intervals.

Statistically significant changes in the hair weight was found using both the standard alcohol minoxidil preparation and the liposomal preparation as compared to the controls. The standard alcohol preparation appeared to provide better hair growth but the difference was not statistically significant.

Accordingly, this shows that minoxidil can be released from lipid vesicles such as liposomes.

Example 3

In this example, a variety of formulations were tested in order to determine the most efficacious formulation for delivering minoxidil. Table 1 shows the formulations used in this testing and the initial results.

TABLE 1

	FORMULATIONS	SURFACE & STRATUM CORNEUM	LIVING SKIN STRATA	RECOVERY
I	GDL/HPBCD NOVASOMES	96.39±0.37	0.21±0.05	96.62±0.32
II	GDL/HPBCD/ETOH NOVASOMES	90.85±4.16	0.36±0.11	91.17±4.14
III	GDL/LACTATE NOVASOMES	92.76±3.89	0.75±0.33	93.51±3.56
IV	GDS/HPBCD NOVASOMES	96.21±6.14	0.09±0.03	96.30±6.14
V	GDS/HPBCD/ETOH NOVASOMES	98.89±2.23	0.18±0.05	98.87±2.20
VI	GDS/LACTATE NOVASOMES	90.63±5.82	0.22±0.03	90.86±5.84
VII	GDL/GDS/HPBCD NOVASOMES	84.41±7.73	0.11±0.01	84.52±7.72
VIII	GDL/GDS/HPBCD/ETOH NOVASOMES	92.96±6.01	0.24±0.05	93.20±6.02
IX	HPBCD AQUEOUS SOLUTION	94.44±3.30	0.08±0.03	94.52±3.27
X	HPBCD/ETOH AQUEOUS SOLUTION	99.10±8.99	0.10±0.02	99.21±9.01
XI	LACTATE AQUEOUS SOLUTION	92.99±6.51	0.18±0.01	93.17±6.51
XII	ROGAINE	86.45±2.79	0.35±0.14	86.80±2.66

Deposition of minoxidil (expressed as percent of applied dose ± standard deviation) into various compartments of hairless rat skin 12 hours after *in vivo* topical application of 100 µl various formulations to 2.54 cm² area (n =3-4).

In all formulations, the vesicles were made with a 57:15:28 ratio of primary lipid/cholesterol/secondary lipid. Formula I had vesicles made of glycerol dilaurate (primary lipid), polyoxyethylene 10 stearyl ether (secondary lipid), and cholesterol, with minoxidil formed into a salt with a cyclodextrin (HPBCD). Formula II had the same vesicles and minoxidil, except ethanol was included in the minoxidil formulation. Formula III had the same vesicles with a salt made of the minoxidil using lactic acid/lactate as the salt forming agent. Formula IV is the same as Formula I except the glycerol dilaurate is replaced with glycerol distearate. Formula V is identical to Formula II but, again, the glycerol distearate replaces the glycerol dilaurate. Formula VI is the same as Formula III but again, the glycerol dilaurate is replaced with glycerol distearate. Formula VII has a combination of glycerol dilaurate and glycerol distearate in equal parts as the vesicle forming agent and is otherwise the same as Formula I, while Formula VIII is the same as Formula II except the glycerol dilaurate/glycerol distearate combination is used to replace the glycerol dilaurate. Formula IX is an aqueous solution of the cyclodextrin cross-linking

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agent with the minoxidil so as identical to Formulas I, IV and VII but without the lipid vesicle encapsulation. Formula X is the same as Formulas II, V and VIII except it is lacking the vesicles. Formula XI is the same as Formula III except lacking the vesicles and Formula XII is of an identical composition to the commercial Rogaine® preparation which does not have a minoxidil salt but rather as a solution of minoxidil in a combination of ethanol, propylene glycol and water. This preparation is considered to be the best for delivering minoxidil to hair follicles.

Table 1 shows the deposition of minoxidil (expressed as percent of applied dose \pm standard deviation) into various components of hairless rat skin 12 hours after in vivo topical application of 100 μ l of the various formulations to a 2.54 cm² area. As can be seen from the data shown on this table, Formula III, the glycerol dilaurate/lactic acid vesicles had twice the penetration into the deepest skin strata of any other formulation. The next best were the commercial Rogaine® preparation and the preparation having the cyclodextrin salt and ethanol oxide. What is most interesting is that a simple change from glycerol dilaurate (C₁₂) to glycerol distearate (C₁₈) in the vesicle wall changes the penetration several fold.

To test the formulations, 100 μ l of the formulation including ³H-radiolabeled minoxidil is applied to a 2.54 cm² area of dorsal rat skin. Three to four rats were used for each formulation. At the end of 12 hours, the rat is sacrificed and the minoxidil on the skin surface is harvested by swabbing the skin with water and alcohol/water washes. The stratum corneum is segregated from the rest of the skin by repeated use of scotch tape; the scotch tape stripping the stratum corneum and allowing harvesting of the minoxidil. The minoxidil in the living skin strata (the living epidermis and dermis) is harvested by surgically removing the remainder of the skin under the surface of application and separating the layers. Each of the samples is segregated and a scintillation counter is used to determine the amount of minoxidil.

Table 2 shows that similar results were obtained in tests using various formulations which were deposited into pilosebaceous of hamster ears. The test uses a 50 μ l topical deposition of the formulation onto the hamster ear, and 30 hours thereafter, the pilosebaceous ventral dermis, cartilage and dorsal ear are measured for minoxidil. More particularly, male Syrian hamsters are cyclically provided 14 hours of light and 10 hours of darkness to maximize androgen dependent sebaceous gland activity and control the size of the glands. Food and water is given to the hamsters ad libitum. The animals are anesthetized with 1 ml of a 10 mg/ml phenobarbital solution.

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The test formulation is applied to the ventral side of the ear, typically in 50 μ l doses. The anesthetization is strengthened every two hours, and 3-4 animals are used in each group. The area of the ear exposed to treatment is biopsied with a 8-10 mm circular punch, rinsed with 5 ml HEPES buffer, blotted with tissue, and rinsed with an additional 5 ml of buffer. The full thickness biopsy is then peeled carefully into its constituent layers using forceps. The epidermis is peeled off easily by probing the edge of the membrane with forceps, clamping a loose end, and pulling. The sebaceous glands in the ventral dermis and the cartilage are scraped free with a dull scalpel so as to avoid damage to the surrounding dermis. The pilosebaceous material is removed by first placing the ventral dermis on a glass slide, dermis side up, and scraping more intensely than for cartilage removal. A milky white suspension is collected.

Table 2 shows percentages and, for pilosebaceous region shows actual μ l recovered.

TABLE 2

Ear Compartment	Formulation Type			
	Formula XII- (Rogaine)	Formula I-(Novasome /Cyclodextran)	Formula II-(I+alcohol)	Formula III-(Novasome)
Pilosebaceous (μ g)	0.1 \pm 0.1 (2.65 \pm 1.27)	0.2 \pm 0.1 (3.14 \pm 1.30)	0.2 \pm 0.1 (4.37 \pm 1.92)	0.4 \pm 0.1 (7.54 \pm 1.96)
Ventral Dermis	0	0	0	0
Cartilage	0.3 \pm 0.2	0.4 \pm 0.5	0.3 \pm 0.1	1.8 \pm 1.1
Dorsal Ear	0.5 \pm 0.5	0.2 \pm 0.2	0.2 \pm 0	1.7 \pm 0.7

The formulations used were formulas I, II, III and XII as described previously. As can be seen from the results shown on Table 3, Formula III yields much higher levels of minoxidil in the pilosebaceous, cartilage and dorsal ear than any of the other formulations. The other formulations, while not as good as Formulation III, are all comparable to the Rogaine® formulation XII which is the best commercial formulation for the delivery of minoxidil. Accordingly, any of these formulations would be acceptable.

The foregoing examples illustrate the effectiveness of the present invention. These examples are merely exemplary and those skilled in the art will be able to determine other modifications to the described procedures which fall within the scope of the invention. Accordingly, the invention is defined by the following claims and equivalents thereof.

In the Claims

1. A method of improving the topical penetration into a skin portion having
5 hair follicles of a therapeutic material which is a weak acid or weak base comprising the steps of:

modifying the solubility of said therapeutic material in aqueous solutions to make
said material more hydrophilic without changing the therapeutic properties of said material;
encapsulating said modified therapeutic material in a lipid vesicle; and
10 delivering said lipid vesicle containing said modified therapeutic material to said
skin portion having hair follicles;
whereby said hair follicles act as a conduit for said therapeutic material.

2. The method of claim 1 wherein said step of modifying said therapeutic
15 material comprises ionizing said material by modifying the pH of a solution containing said
material.

3. The method of claim 1 wherein said step of modifying said therapeutic
material comprises forming a salt of said therapeutic material.
20

4. The method of claim 3 wherein said step of forming a salt comprises the
step of reacting said therapeutic material with an organic acid or base.

5. The method of claim 4 wherein said organic acid comprises an alpha-
25 hydroxy acid, or a pharmaceutically acceptable salt thereof.

6. The method of claim 5 wherein said alpha-hydroxy acid comprises lactic
acid, or a pharmaceutically acceptable salt thereof.

7. The method of claim 3 wherein said step of forming a salt comprises the
30 step of reacting said therapeutic material with a dextrin.

8. The method of claim 7 wherein said dextrin comprises a cyclodextrin.

9. The method of claim 1 wherein said lipid vesicle comprises a non-
35 phospholipid as the primary wall material.

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10. The method of claim 9 wherein said lipid vesicle comprises a primary wall material selected from the group of non-phospholipids consisting of C₁₂-C₁₈ fatty alcohols, C₁₂-C₁₈ glycol monoesters, and C₁₂-C₁₈ glycerol mono-and diesters.

5 11. The method of claim 1 wherein said therapeutic material comprises minoxidil or a therapeutically effective derivative thereof.

12. A method of providing improved topical penetration of minoxidil, or a therapeutically effective derivative thereof, comprising the steps of:

10 reacting said minoxidil or a pharmaceutically acceptable derivative thereof with an organic acid or a salt of an organic acid;

encapsulating said reaction product in a non-phospholipid lipid vesicle; and

topically applying said encapsulated minoxidil reaction product to a skin location having hair follicles thereon;

15 whereby topical penetration is primarily achieved via said hair follicles.

13. The method of claim 12 wherein said organic acid comprises lactic acid.

14. The method of claim 13 wherein said non-phospholipid lipid vesicle
20 comprises a primary wall material selected from the group consisting of C₁₂-C₁₈ fatty alcohols, C₁₂-C₁₈ glycol monoesters, and C₁₂-C₁₈ glycerol mono-and diesters.

15. The method of claim 14 wherein said primary wall material comprises glycerol dilaurate.

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16. The method of claim 15 wherein said lipid vesicle further comprises polyoxyethylene 10 stearyl ether.

17. The method of claim 16 wherein said lipid vesicle further comprises a sterol
30 selected from the group consisting of cholesterol, phytosterol, and pharmaceutically acceptable derivatives thereof.

18. A pharmaceutical preparation for treatment of hair loss comprising a pharmaceutically acceptable salt of minoxidil encapsulated in a non-phospholipid lipid
35 vesicle.

19. The preparation of claim 18 wherein said non-phospholipid lipid vesicle comprises a primary lipid in its wall structure selected from the group consisting of C₁₂-C₁₈ fatty alcohols, C₁₂-C₁₈ glycol monoesters, and C₁₂-C₁₈ glycerol mono-and diesters.

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20. The preparation of claim 19 wherein said primary wall material comprises glycerol dilaurate.

5 21. The preparation of claim 21 wherein said lipid vesicle further comprises polyoxyethylene 10 stearyl ether.

22. The preparation of claim 21 wherein said lipid vesicle further comprises a sterol selected from the group consisting of cholesterol, phytosterol, and pharmaceutically acceptable derivatives thereof.

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23. The preparation of claim 18 wherein said non-phospholipid lipid vesicle comprises a paucilamellar lipid vesicle.

15 24. The preparation of claim 18 wherein said pharmaceutically acceptable salt of minoxidil comprises a reaction product of minoxidil and an organic acid or a salt of an organic acid.

25. The preparation of claim 25 wherein said organic acid or salt of an organic acid comprises an alpha-hydroxy acid.

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26. The preparation of claim 26 wherein said alpha-hydroxy acid is selected from the group consisting of lactic acid, lactate, and derivatives thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/15686

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/127

US CL :424/450

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450; 514/880

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 5,030,442 A (USTER et al.) 09 July 1991, abstract, columns 4-8, examples and claims.	1-4, & 11 ----- 5-6, 9-10, 12-20 & 22-27
Y	US 5,422,370 A (YU et al.) 06 June 1995, column 2, lines 3-68 and examples 3 and 4.	5, 6, 13-17 & 26-27
Y	DOWTON et al. Influence of liposomal composition on topical delivery of encapsulated cyclosporin A I. An in vitro study using hairless mouse skin. S.T.P. PHARMA SCIENCES. 1993, Vol. 3, No 5, Pages 404-407, especially pages 405 and 406.	5-6, 9-10 & 12-20, 22-27



Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,032,457 A (WALLACH) 16 July 1991, columns 1-5, and examples.	9-10, 12-20, 22-27
A	MANOSROI et al., THERMODYNAMIC CHARACTERISTICS OF A HUMAN INSULIN-DEAE-DEXTRAN COMPLEX ENTRAPPED IN LIPSOMES. DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY. 1990, Vol. 16, No. 5, pages 837-854.	7, 8